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Arnold Hoffman

HOFFMAN9

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER

ANDERSON, JAMES D

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/621,326

Applicant(s)

HOFFMAN ET AL.

Examiner

James D. Anderson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 November 2007 and 13 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4,7,8 and 10-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 7, 8, and 10-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/ are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1, 4, 7, 8, and 10-27 are presented for examination

Applicants' amendment filed 11/5/2007 and Supplemental Amendment filed 11/13/2007 have been received and entered into the application. Accordingly, claim 1 has been amended and claims 26-27 have been added.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejection being applied against the pending claims, this Office Action is **Non-Final**.

Status of the Claims

Newly added claim 26 finds support in the originally filed claims and at page 14, lines 1-2 of the specification wherein the specific treatment of tumor cells having an operative RB protein is disclosed.

Response to Arguments

Applicant's arguments filed 11/5/2007 have been fully considered but they are not persuasive. Applicants present the following arguments.

First, with respect to the 35 U.S.C. 112, 1st Paragraph (Scope of Enablement) rejection of claims 1, 4, 7, 8, 10-21, and 24, Applicants argue that the present invention uses known classes

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of compounds, but uses them in a novel combination and administering them with a novel protocol in order to obtain unexpected results of the present invention. Thus, one of ordinary skill in the art would not need to discover what compounds cause oxidation of GSH because this is a known class of compounds and those of ordinary skill in the art are in possession of this class of compounds without any experimentation. However, this line of argument appears to be directed to a written description as opposed to the present scope of enablement rejection and is thus not applicable to the present rejection.

Second, Applicants discuss the mechanism through which the present invention works to treat tumors. The Examiner fails to see how the mechanism of the present rejection relates to the present scope of enablement rejection. The instantly claimed methods require combining at least two agents selected from four different classes having four different mechanisms of action. However, the originally filed disclosure only teaches and provides direction for a specific combination of three active agents (*i.e.*, BSO, disulfiram, and BCNU). No actual data is presented showing that this combination is effective to treat any tumors, let alone the full scope of tumors encompassed by the claims. Applicants present three 37 C.F.R. Declarations to support enablement of the claimed invention. The 37 C.F.R. 1.132 Declaration of Sanford Sampson (Sampson Declaration) provides experimental results for a specific combination of four active agents (*i.e.*, disulfiram, BCNU, BSO, and curcumin) in 3T3 fibroblasts, pancreatic and prostate cancer cells, and bladder tumor cells. The 37 C.F.R. 1.132 Declaration of Lee Spetner (Spetner Declaration) provides data for the same combination drugs tested in the Sampson Declaration. In these experiments however, Mx-1 breast cancer cells were treated. The 37 C.F.R. 1.132 Declaration of Arnold Hoffman (Hoffman Declaration) provides data for the same

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combination drugs tested in the Sampson and Spetner Declarations. In these experiments however, bladder tumors were treated. Thus, the data submitted by Applicants shows that a specific combination of four specific drugs are effective in inhibiting cell proliferation in 3T3 fibroblasts, pancreatic and prostate cancer cells, bladder tumor cells, and breast cancer cells. Accordingly, the claims are deemed enabled for treating tumors with the specific combination of disulfiram, BCNU, BSO, and curcumin. However, the claims encompass thousands of possible drug combinations, ranging from administering a single drug that decreases the $[GSH]^2/GSSG$ ratio in malignant cells to “at least two agents” selected from four different classes of compounds having four different mechanisms of action. There is no evidence of record that the efficacy observed with the specific combination tested by Applicants would also be observed with other drug combinations encompassed by the claims. The specification presents a hypothesis that combinations of drugs having different mechanisms of action can be combined to decrease the $[GSH]^2/GSSG$ ratio in malignant cells. However, only four specific compounds were actually tested in combination in five specific tumor cells. As such, the results presented by Applicants in the Sampson, Spetner, and Hoffman Declarations are not seen as being commensurate in scope with the claimed methods of treatment. As such, it would take an undue amount of experimentation to determine which other drugs or drug combinations might be effective in treating the claimed tumors. This is especially true given the fact that drugs have similar mechanisms of action are not, *a priori*, effective in treating the same cancers.

Third, with respect to the 35 U.S.C. 102(a) rejection of claims 1, 4, 7, 8, and 10-25, Applicants argue that the Hoffman PCT publication is not available as a prior art reference under 35 U.S.C. 102(a) as it is an invention by another. In support of this argument, Applicants attach

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a declaration by the present inventors "clarifying" the inventive entity named in the PCT application was erroneous and has been corrected by the filing of the present CIP application. However, there are two problems with this line of argument. First, Applicants removed the claim to priority to the Hoffman PCT application (PCT/IL02/00051, published as WO 02/056823). Second, the USPTO has nothing to do with correcting inventorship in PCT applications. As such, until either 1) the inventorship in the PCT application is corrected through WIPO or 2) the inventorship in the present application is changed, WO 02/056823 is available as prior art under 35 U.S.C. 102(a) as it is an invention "by another" published prior to the filing date of the present application.

Fourth, with respect to the 35 U.S.C. 103 rejection of claims 1, 4, 7, 8, and 10-25 as being unpatentable over USP 6,589,987 in view of Huang, Ali-Osman, and Nagendra, Applicants argue that the prior art references do not suggest the present invention. In support of this argument, Applicants state that while USP 6,589,987 discloses administration of disulfiram to inhibit the growth of cancer cells, disulfiram does not decrease proliferation through redox mechanisms. However, the mechanism through which disulfiram acts is inconsequential to the present rejection. USP 6,589,987 suggests administering disulfiram to treat cancer and further suggest that it can be combined with other anticancer agents. It is noted that disulfiram recited as an agent that causes oxidation of GSH in the instant claims (claims 1 and 7). With respect to Huang, Applicants assert that Huang does not teach that BSO would be useful as an anticancer agent. However, Huang explicitly teaches that administration of BSO to hepatocellular carcinoma cells decreases GSH levels and rates of growth. With respect to Ali-Osman, Applicants present no specific arguments other than reiterating that Ali-Osman suggests that

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BSO may sensitize cell lines to treatment with carmustine (BCNU). Nagendra teaches that disulfiram decreases [GSH] and perturbs $[GSH]^2/GSSG$ redox status. Because this is exactly what is being claimed (*i.e.*, administering an agent that causes a decrease in the $[GSH]^2/GSSG$ ratio), Nagendra clearly relates to the claimed invention. Applicants conclude that the four references do not teach the mechanism of action that is required by the present claims. However, as noted *supra*, the mechanism of action is inconsequential to the present rejection. The prior art references teach and suggest that disulfiram, BSO, and carmustine could be useful in the treatment of cancer cells. As such, in the absence of a showing of unexpected results commensurate in scope with the claims, combining these drugs to treat tumors would have been *prima facie* obvious, regardless of their mechanism of action. Upon further consideration, the combined prior art does not teach the limitations of claims 17-20. However, Hoffman *et al.*, newly applied in the rejection set forth below, does suggest the limitations of claims 17-20 and further suggests the limitations of new claim 26.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 7-8, 10-21, 24, and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of tumors with disulfiram, BSO carmustine (BCNU), and curcumin, does not reasonably provide enablement for the treatment of tumors with the broad genera of agents contemplated by the instant claims. The specification

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does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).¹

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,

¹ As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

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- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of tumors having an operative protein retinoblastoma protein comprising administering combinations of agents that include: (i) agents that oxidize GSH; (ii) agents that form adducts of conjugates with GSH; (iii) agents that inhibit the GCS enzyme; and (iv) agents that inhibit the GR enzyme. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

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factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an

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area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 26) vary broadly, reciting the treatment of tumors having an operative protein retinoblastoma protein with any agent that causes a decrease in the $[GSH]^2/[GSSG]$ ratio. Others, such as claims 8 and 11, are narrower, reciting specific species of the claimed genera of compounds. All, however, are extremely broad insofar as they disclose the general treatment of malignant tumors with having an operative protein retinoblastoma protein with single active agents or combinations of active agents selected from four broad genera of compounds defined only by biological activity.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. In fact, the specification is purely prophetic and theoretical in nature. Applicants theorize that the claimed combinations of active

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agents will be useful in the treatment of tumors purely based on their individual mechanisms of action. The direction concerning treating tumors is found in the specification at pages 24-30, which merely states applicants' intention to do so by providing an *in vivo* assay for determining the tumor growth inhibitory effect of the claimed compounds. No compounds were actually tested in this assay. Applicants describe formulations at page 25, which only describes known routes of administration. Doses required to practice their invention are described at page 27, but only for three specific drugs (BSO, disulfiram, and carmustine). There is an *in vivo* assay described in pages 24-25 (with no data) and it is unclear if this assay correlates to all of the tumors encompassed by the claims. There is no working example of treatment of any tumor in cells, animals or man. 37 C.F.R. 1.132 Declarations filed by Arnold Hoffman, Lee Spetner, and Sanford Sampson demonstrate that a specific combination of active agents is effective in treating 3T3 fibroblasts; pancreatic and prostate cancer cells, bladder tumor cells, and breast cancer cells. However, there is no evidence of record that this efficacy can be predictably extended to any other agents having the claimed mechanisms of action. Further, while Applicants define the nature of the claimed active agents, inhibition of an enzyme does not predictably correlate to clinical efficacy. Thus, there are no working examples correlating the biological activity of the claimed active agents with efficacy in the treatment of tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combinations could be predictably used as a

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treatment for all malignant tumor growth as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that apoptosis of malignant cells can be achieved by increasing the intracellular redox potential, E , above E_{CCP} , and maintaining this higher E for an appropriate duration of time such as to induce selective apoptosis of cancer cells. However, the claims encompass a multitude of compounds, defined only by biological activity, having a plethora of chemically and biologically distinct substituents. The idea that combining such compounds will, *a priori*, lead to an effective treatment of all malignant tumors is simply beyond the scope of the present invention.

Determining if any particular claimed compound or combination of compounds would treat any particular malignant tumor would require formulation into a suitable dosage form and subjecting such compounds or combination of compounds to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants taken together with the extremely broad scope of the claims. Further, as noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

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Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4, 7-8 and 10-27 are rejected under 35 U.S.C. § 102(a) as being anticipated by **Hoffman** (WO 02/056823) (cited by applicants in IDS filed 2/13/2007).

Hoffman teaches a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). Treatment of tumors is taught at page 7, lines 25-32. The treatment of tumors having an operative RB protein as recited in claim 26 is taught at page 7, lines 22-24. GSH depleting agents include oxidizers of GSH (*e.g.*, α -lipoic acid, hydrogen peroxide, ascorbic acid, quinones), agents that form adducts with GSH (*e.g.*, Michael acceptors), and inhibitors of GSH (*e.g.*, BSO) (pages 9-10). These are the same agents recited in instant claims 1, 7, 8, 11, 13, 21-23 and 25. Combination with standard chemotherapeutics as recited in instant claim 4 is taught at page 11, line 30 to page 12, line 4. Hoffman teaches combinations comprising more than one GSH-depleting agent as recited in the instant claims (page 13, line 10 to page 14, line 6; page 16, line 5 to page 17, line 18; page 19, lines 11-33). With respect to the instantly claimed functional

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limitations (e.g., “such that” clauses in claims 1 and 17-20), it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to “prove that subject matter to be shown in the prior art does not possess the characteristic relied on” (205 USPQ 594). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) (“[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention”).

Accordingly, for the above reasons, the claims are deemed properly rejected.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 4, 7-8 and 10-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** (Issued July 8, 2003; Filed Sept. 8, 1999) in view of **Huang *et al.*** (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020), **Nagendra *et al.*** (Alcohol, 1994, vol. 11, pages 7-10) and **Hoffman *et al.*** (J. Theor. Biol., 2001, vol. 211, pages 403-407) (prior art of record).

The instant claims are drawn to the treatment of tumors comprising administering the elected species disulfiram (oxidizes GSH), buthionine sulfoximine (BSO; inhibits GCS enzyme) and carmustine (BCNU; inhibits GR enzyme). Applicants claim that administration of “at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio” in the malignant cells of the tumor will lead to treatment of said tumor in a subject (see instant claims 26-27). The addition of Hoffman *et al.* to this rejection is necessitated by Applicants' new claim 26, which recites the treatment of tumors having an operative protein retinoblastoma protein. Hoffman *et al.* also suggest the limitations of claims 17-20, which were not properly addressed in the previous Office Action.

'987 discloses that disulfiram inhibits the growth of cancer cells (Abstract; col. 2, lines 38-44). Disulfiram can also be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18). It is noted that disulfiram is an agent that causes oxidation of GSH (see instant claim 25). The primary reference is silent with respect to BSO and BCNU.

Huang *et al.* disclose that the glutathione (GSH) level in hepatocytes increases during active proliferation (Abstract). The authors evaluated whether a similar increase is found in

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hepatocellular carcinoma (HCC). It is disclosed that GSH levels doubled in HCC as compared to normal liver (page 19). HepG2 liver cancer cells were grown with varying concentrations of cysteine and it was found that cell growth increased with increasing cysteine concentration (page 19, right column). Further, BSO treatment decreased GSH levels and rates of growth. Cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls (page 19, right column). The authors disclose that GSH has been found to be elevated in a number of drug-resistant tumor cell lines including prostate, ovarian, lung and colorectal cancers (page 20, right column), thus suggesting that a decrease in GSH as achieved with BSO may result in a decrease in cell growth. Increased γ -L-glutamyl-L-cysteine synthetase (GCS) activity was found in the majority of these resistant tumor cells. The authors conclude that “an increase in the cellular GSH content may change the thiol-redox status of the cell that is proportional to $[GSH]^2/[GSSG]$ ” (page 21, right column). This change in redox state may then “affect the expression or activity of factors important for cell cycle progression”. It is noted that BSO is recited as an agent that causes inhibition of the GCS enzyme (see instant claim 25). The secondary reference is silent with respect to disulfiram and BCNU.

Ali-Osman *et al.* disclose that depletion of GSH by BSO (currently being explored as a means of enhancing the efficacy of cancer chemotherapy and explicitly taught in Huang *et al.*) in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme (see instant claim 24). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell

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lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The tertiary reference is silent with respect to disulfiram.

Nagendra *et al.* disclose that chronic administration of disulfiram to rats affects GSH metabolism (Abstract). Administration of disulfiram led to a decrease in GSH with a concomitant increase in GSSG content, which would thus result in a decrease in the $[GSH]^2/[GSSG]$ ratio as instantly claimed. Brain glutathione reductase activity was also significantly depleted. The authors conclude that treatment with disulfiram decreases GSH content with a concomitant increase in GSSG level and perturbs the GSH/GSSG redox status, inducing oxidative stress on the brain. As Nagendra *et al.* is cited only for this general teaching, it follows that it is silent with respect to treating tumors.

Hoffman *et al.* is cited for the general teaching that an elevated redox potential has been observed to be associated with the inability of retinoblastoma (RB) protein to be phosphorylated and with cell cycle arrest. As such, the authors suggest that an elevated redox potential can inhibit phosphorylation of RB protein, which in turn will stop cell proliferation (page 403, paragraph bridging left and right columns), thus suggesting the treatment of cancers having an operative retinoblastoma (RB) protein via changes in redox potential. Hoffman *et al.* further teach that application of agents that decrease GSH will increase redox potential (page 405, right column, second paragraph under the heading "Model"). For example, Hoffman *et al.* teach that addition of BSO (which is taught by Huang *et al.* to decrease GSH) to fibroblasts and fibrosarcoma cells results in a threshold potential of between -196 and -218 mV that resulted in

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cessation of cell proliferation (page 406, left column, first paragraph under the heading "Application of the Model to Interpreting Published Data), thus suggesting the limitations of claims 17-20.

In view of the above disclosures, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is well known in the art that administration of BSO depletes GSH content and enhances the cytotoxicity of BCNU. Further, disulfiram has been shown to inhibit cancer cell proliferation and decrease GSH with a concomitant increase in GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in instant claim 26). It would have been obvious to combine disulfiram, BSO and carmustine (BCNU) to treat tumors because from the disclosures of the '987 patent, Huang *et al.*, Ali-Osman *et al.* and Nagendra *et al.* it is clear that disulfiram is effective at inhibiting cancer cell proliferation and that decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug BCNU. Thus, the skilled artisan would be imbued with at least a reasonable expectation that administering disulfiram would decrease GSH, increase GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in the instant claims), and be an effective treatment for tumors. In addition co-administration of BSO would be predicted to further decrease GSH content resulting in the sensitization of tumors to BCNU treatment.

Although ample motivation to combine the references is found in the teachings of the individual references as discussed *supra*, disulfiram and carmustine (*i.e.* BCNU) are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for

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the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Further, the addition of BSO to a composition of disulfiram and BCNU would have been obvious given the teachings of Ali-Osman *et al.* who disclose that BSO enhances the anticancer activity of BCNU.

Applicants have offered that because the references do not teach or suggest that the $[GSH]^2/[GSSG]$ ratio be maintained in the malignant cells continuously for about 15 to about 75 hours, the present rejection is not proper. The examiner cannot agree that such provides a patentable distinction. See MPEP § 2144 under the heading, "Rationale Different From Applicant's is Permissible" where it is set forth that, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972)". In both the prior art and the present claims, the ultimate treatment of tumors is or would have been expected. Also, in both the prior art and the present claims, the active

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agent(s) are administered in effective amounts to treat cancer and/or tumors. Further, Huang *et al.* teach that cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls. As such, there is clear motivation to maintain contact of the active agents with tumor cells for the time period recited in the instant claims. Further, one skilled in the art applying the combined active agents suggested by the prior art would continue to apply the active agents until a therapeutic result is achieved.

Modifying administration regimens, doses, length of administration, etc. in order elicit optimal treatment of tumors are all well within the purview of the skilled artisan. Applicant's observation as to why the claimed combinations are effective is not an act of invention because Applicants are not manipulating the active agents in any different manner than is taught and/or suggested by the prior art and do not provide for an ultimate effect that is not taught by or suggested by the prior art. Further, with respect to the redox potentials recited in claim 17-20, such changes in redox potential would be a natural result of administering the combination of active agents suggested by the prior art. In other words, there is no evidence of record that administering the combination of disulfiram, BSO, and BCNU as suggested by the prior art would not result in an increase of redox potential to above about -200 mV or between about -200 mV and -190 mV as instantly claimed. In fact, as noted *supra*, Hoffman *et al.* teach that addition of BSO to fibroblasts and fibrosarcoma cells results in a threshold potential of between -196 and -218 mV which results in cessation of cell proliferation.

Accordingly, for the above reasons, the claims are deemed properly rejected.

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, 7-8 and 10-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-20 and 25-28 of copending Application No. 11/596,043. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of inducing apoptosis in

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cancerous cells as claimed in the '043 application reasonably encompass the "treatment" of tumors as instant claimed.


This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


James D. Anderson
Patent Examiner

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January 18, 2008

Ardin H. Marschel 1/19/08

**ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER**